ICH E21 EWG: Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials

Step 2 document – to be released for comments

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

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Background

- This document has been signed off as a *Step 2* document (14 May 2025) to be issued by the ICH Regulatory Members for public consultation.
- This document was developed based on a Concept Paper (11 June 2023).
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: Q1 2028.

Guideline Objectives

- The objective of this guideline is to provide recommendations for the appropriate inclusion and/or retention of pregnant and/or breastfeeding individuals in clinical trials and facilitate the generation of robust clinical data that allow for evidence-based decision making on the safe and effective use of medicinal products by these individuals and their healthcare providers (HCPs).

Guideline Scope

- The scope of this guideline includes pre- and postmarketing clinical trials of investigational products (see ICH E6(R3)) for indications in the general population and indications specific to pregnant or breastfeeding individuals.

Key Principles (1/3)

- In principle, inclusion of pregnant and breastfeeding individuals in clinical trials should be considered for all products where individuals of childbearing potential are among the anticipated user population. It is especially important for conditions where there is high unmet medical need for treatment in pregnancy or while breastfeeding; however, the scope of this guideline is not limited to these scenarios.
- Proactive planning for obtaining data and data collection related to use in pregnancy and/or breastfeeding through nonclinical and clinical studies (or the rationale for not obtaining data) should be done from the early stages of formulating the development strategy for the investigational product.

Key Principles (2/3)

- Recommend to consult with regulatory authorities as early as possible and as needed throughout the investigational product development process.
- Recommend early engagement with appropriate stakeholders, including patients.
- Every effort should be made to reduce the burden of study procedures on pregnant and breastfeeding study participants.
- Essential to avoid any undue influence or coercion when pregnant or breastfeeding individuals are included in clinical trials.
- Assessing the safety in pregnant and breastfeeding individuals is complex as there are potential impacts on the fetus and breastfed child to consider.

Key Principles (3/3)

- Ongoing safety monitoring of product use in these populations in the postmarketing period contributes to the identification of safety signals, especially for rare or delayed outcomes, that are unlikely to be thoroughly addressed in pre-authorization clinical trials.
- Available data and assessment of investigational product benefits and risks during pregnancy and breastfeeding are expected to be included and updated as necessary in labeling documents.

Ethical Considerations

- Inclusion of pregnant and breastfeeding individuals in clinical trials is ethical and supported by the Declaration of Helsinki and ICH Guidelines (ICH E6(R3) and ICH E8(R1))
- Consideration should be given to the use of Institutional Review Boards (IRBs) or Ethics Committees (ECs) experienced in working with pregnant and breastfeeding participants.

Pregnancy – Development Strategy

- Sponsors should anticipate that the approach to include pregnant individuals in clinical trials will require careful assessment of benefits and risks that may evolve depending on multiple factors, including the stage of clinical development, the duration of treatment, the indication being sought, and the strength of the available evidence.
- The approach may differ based on the anticipated trimester of pregnancy of participants to be included in the clinical trial.

Pregnancy – Key Points to Consider for Data Collection

- Incorporating evidence collection for pregnant individuals into the development strategy starts with considering the targeted condition, patient population, and existing treatments.
- Sponsors should consider how pregnancy might affect the disease state (e.g., potential worsening of the disease/condition if under- or untreated), as well as how the patient's disease (and its treatment) could impact the pregnancy and its outcomes (e.g., the potential increase in risk of adverse pregnancy outcomes due to inadequate disease control).
- Physiological changes may affect absorption, distribution, metabolism, and elimination.
- Data need to be collected as early as possible during product development based on above considerations.
- Sponsors are encouraged to evaluate and update the development strategy as new information or data become available.
- Development strategy should aim for early acquisition of data from pregnant individuals unless there exists justification for postponement.

Pregnancy – Evidence Needed to Support Inclusion

- The data and evidence needed to support the decision to include pregnant individuals in a clinical trial or to enable ongoing participation of individuals who become pregnant will depend on a weight of evidence approach and consideration of the following:
  - The indication and the intended population;
  - Nonclinical data;
  - The prospect of benefit;
  - The clinical pharmacology of the investigational product;
  - Biological plausibility of harm due to pregnancy exposure;
  - When during the pregnancy the investigational product would be administered;
  - The novelty of the investigational product (i.e., the availability of data from molecular entities or treatments similar to the investigational product).

Pregnancy – Nonclinical Data

- Prior to proceeding to studies including pregnant individuals, the results from relevant nonclinical studies need to be evaluated.
  - Standard Developmental and Reproductive Toxicology (DART) studies (see ICH M3 and ICH S5);
  - Standard genotoxicity studies (if relevant, See ICH S2);
  - Appropriately qualified/validated tests;
  - Any relevant modeling;
  - Note: Timing and necessity for DART studies may be influenced by characteristics of investigational product (IP), clinical indication, or intended patient population;
  - If risks are identified, additional investigations may be warranted.

Pregnancy – Benefit-risk Assessment and Next Steps

- When the necessary nonclinical and clinical data become available, the sponsor should perform a benefit-risk assessment that incorporates all relevant information, using a weight of evidence approach. The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy are reasonable given the anticipated benefits.
  - If the sponsor determines that proceeding with trials in pregnancy is not yet reasonable, they should seek to obtain further data unless there is a rationale for not studying the investigational product in pregnancy.
    - For some investigational products, the benefits of use in pregnancy may still outweigh the potential risks. Examples include situations where the target disease has a serious negative or where available treatment(s) have a safety concern in pregnancy.
  - If the sponsor determines that proceeding with trials in pregnancy is appropriate, then the following approaches/actions (in no specific order) need to be considered and/or incorporated into the development strategy:
    - Recruitment of pregnant individuals into ongoing and/or subsequent clinical trials;
    - Removal of mandatory contraception requirements in ongoing and/or subsequent clinical trials;
    - Ongoing participation of individuals who become pregnant during clinical trials;
    - Implementation of study(ies) specifically designed to be conducted in pregnant individuals if needed.

Pregnancy – Inclusion in Clinical Trials (1/2)

- Study design and safety impact on the pregnancy by all products used within the trial (i.e., test and comparator products) should be considered.
- Additional endpoints (e.g., PK/PD data) or alternate end-points if the methodology has an inherent risk to the pregnancy (e.g., CT-scans) may also need to be considered for pregnant participants.
- Participants should be closely monitored for pregnancy-related adverse events (AEs), with appropriate management plans if required.

Pregnancy – Inclusion in Clinical Trials (2/2)

- Assessments and Data Collection for Pregnant Participants and Infants:
  - In addition to standard reporting requirements and Good Clinical Practice (GCP) (see ICH E6(R3)), additional outcome parameters may be considered, with attention to the disease/condition being treated by the investigational product, investigational product properties, duration of use, and therapeutic context.
  - The duration of infant follow-up should be considered on a case-by-case basis.
  - The duration of infant follow-up should take into consideration that birth defects and functional or neurodevelopmental disorders may be diagnosed beyond birth.

Pregnancy – Recruitment and Retention

- Engaging with patients' advocacy groups, organizations managing disease specific registries, and clinicians experienced in conducting research in pregnant individuals before clinical trial initiation may help reduce challenges to recruitment or barriers to participation.
- The additional time required for follow up of pregnancy and infant outcomes, may mean that additional efforts are needed to support retention of participants.

Pregnancy – Informed Consent

- The consent form should clearly state whether ongoing participation will be allowed during pregnancy and, if so, under what conditions.
- Should reflect the potential benefits and risks of the investigational product as applicable in the intended pregnancy trimester(s) of exposure.
- Participants who have a confirmed pregnancy while enrolled in a clinical trial should be provided with information to make an informed decision for both themselves and their fetus.
- Additional circumstances for reconsent:
  - When mandatory contraceptive requirements of the trial have been removed while the trial is ongoing.
  - When new information changes the benefit-risk assessment for the pregnant participant or their fetus.

Breastfeeding – Development Strategy (1/2)

- The benefit-risk considerations for medicinal product use during breastfeeding involve multiple factors, such as the amount of investigational product present in breastmilk, the extent of absorption by the child, the potential benefits and risks of the medicine for the patient and the breastfed child, available treatment alternatives, the benefits of breastfeeding, and available alternatives to breastfeeding.
- **ICH E21 includes discussion on the following:**
  - Obtaining information on the transfer of investigational product into breastmilk (either without or with investigational product exposure to the infant);
  - Subsequently, inclusion of breastfeeding individuals in clinical trials in the general population after the investigational product's characteristics related to breastfeeding have been determined.

Breastfeeding – Development Strategy (2/2)

- The clinical development strategy for investigational product use in breastfeeding should be tailored to the stage of development and existing knowledge about the investigational product.
- Since investigational product exposure to the infant can be avoided by replacing breastmilk with formula or other supplemental nutrition, whether and, if so, when to allow such exposure during development must be carefully considered.
- Sponsors should anticipate if, and when, clinical trials involving breastfeeding individuals may be initiated and plan to conduct studies to gather information on exposure levels and effects on a breastfed child if needed as early as possible in development.

Breastfeeding – Evidence Generation

- Data collection relevant to breastfeeding can be broadly categorized into the following steps:
  - Determine the concentration of investigational product in breastmilk (relative to maternal therapeutic blood levels),
  - Use breastmilk concentration data for estimation of the daily infant dose and relative infant dose, and
  - Collect infant exposure, safety, and benefit data, as applicable.

Breastfeeding – Nonclinical

- Nonclinical studies may be used to generate data on lactational exposure to an investigational product.
  - Standard pre- and postnatal development (PPND) study (see ICH S5).
  - Juvenile toxicology study with direct dosing of juvenile animals can be used to further characterize potential risks (see ICH S11).
  - Qualified/validated alternative assays (ICH S5) may also be used to generate lactational exposure data.
  - Appropriate use of modeling techniques, such as physiologically based pharmacokinetics (PBPK) modeling, may provide insights into likely levels of an investigational product in breast milk and subsequent infant exposure, absorption, and metabolism (see ICH M15).

Breastfeeding – Lactation Studies (Maternal-only)

- Studies that assess product levels in maternal milk with no infant exposure to investigational product through breastmilk (i.e., maternal-only studies).
  - These studies are usually conducted in breastfeeding patients but, when necessary, can be conducted in breastfeeding healthy volunteers.
  - In both cases, the participant must pump and discard the breastmilk.
  - Lactation studies evaluating investigational product levels in breastmilk provide detailed information about the amount/concentration and duration of an investigational product in breastmilk.

Breastfeeding – Lactation Studies (Mother-infant Pair)

- Studies that assess IP levels in the maternal milk as well as in the infant exposed through breastmilk
  - This includes opportunistic studies which recruit patients who are already on a marketed medication based on clinical need and choose to continue treatment during breastfeeding, stand-alone lactation studies, and lactation studies conducted within clinical trials where breastfeeding individuals are enrolled along with the general population.
  - For lactation studies in which the infant is exposed to the investigational product and that are not opportunistic in design, data are needed to support a favorable benefit-risk profile in the infant.

Breastfeeding – Inclusion in Clinical Trials

- The inclusion of breastfeeding individuals in clinical trials for indications in the general population may be permissible with the appropriate data available and considerations for benefit-risk for both the mother and the child.
- When there is reasonable scientific assumption that the investigational product may not be meaningfully absorbed from breastmilk or the potential benefits for mother and infant outweigh any potential risk to the infant, the protocol could allow a choice for participants to keep breastfeeding.

Breastfeeding – Inclusion in Clinical Trials

- When both the mother and the infant are exposed to the investigational product, uptake of the product in the infant needs to be understood (or evaluated, if necessary), at relevant timepoints.
- Discontinuation and suspension of treatment
  - The protocol should outline criteria for discontinuing breastfeeding in case of emerging safety concerns to the breastfed child.
  - Consideration should be given whether adjustments to the breastfeeding strategy (e.g., timing or pump and discard) could serve as effective measures to ensure infant safety.

Breastfeeding – Recruitment and Retention

- Recruitment strategies
  - May differ depending on whether enrollment is for lactation studies or for clinical trials.
  - Early consideration of how and when to engage with potential participants may enhance the ability to recruit participants to relevant studies to obtain clinically relevant information on investigational products.
- Reduction of burden
  - Flexibility can reduce the burden on participants.
  - Early and avoidable discontinuation of participants can be mitigated by recognition and support of the challenges of this period.

Breastfeeding – Informed Consent

- In a lactation study where the infant is not exposed to the investigational product, the participant should be advised about the duration that the investigational product will be present in breastmilk to avoid inadvertently exposing the breastfed child to the investigational product.
- Depending on the study design, informed consent may need to consider the potential benefit and exposure risk to the mother and the infant, and risks related to study procedures for the mother and the infant (e.g., breastmilk sampling or blood draws).
- Participants should be reconsented if new information that changes the assessment of benefits and/or risks.

Considerations

- In alignment with the principles of ICH E8(R1), the approach to collecting data from pregnant individuals in clinical trials involves a systematic expansion of data collection across relevant sources and patient populations, guided by data-driven decisions to safeguard study participants.
- General principles for clinical trial conduct and informed consent of ICH E6(R3) apply to pregnant and breastfeeding individuals.
- Standard general recommendations on safety evaluation such as classification, assessment, and reporting of AEs (i.e., ICH E2A, ICH E2F, ICH E6(R3), ICH E8(R1)) apply to studies including pregnant and/or breastfeeding participants.

Conclusions

- A new Efficacy Guideline to provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials.
- To ensure the appropriate inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials conducted to study product safety, efficacy, and dose/dosing regimens in these populations, this global harmonized Guideline will address scientific and high-level regulatory principles.

Contact

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